Prognostic relevance of ultra-early doppler sonography in acute ischaemic stroke: a prospective multicentre study

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Summary

Background **Ischaemic stroke can result from a temporary or permanent occlusion of intracranial arteries. In the hyperacute stage of the disease cerebrovascular ultrasound can be used to determine the vascular pathology, but the significance of very early findings on ultrasound is unclear. The present study aimed to assess the prognostic value of doppler ultrasonography within the first hours after stroke for functional outcome.**

Methods **In a prospective multicentre design, patients with clinical signs of ischaemic anterior-circulation stroke were examined by doppler ultrasonography of the intracranial and extracranial arteries. Patients were separated into three groups according to the findings: normal middle-cerebral artery (MCA); branch occlusions; or a main-stem occlusion. The primary endpoint was functional outcome at 3 months. Logistic regression was used to test the association between the ultrasound diagnosis and functional outcome.**

Results **361 patients were identified with moderate to severe clinical deficits (National Institutes of Health Stroke Scale score 5–25). Of these, 121 (34%) had a normal MCA, 176 (48%) had branch occlusions, 7 (2%) had severe MCA stenosis, and 57 (16%) had a main-stem occlusion. 50 of the 57 (88%) patients with main-stem occlusion were dead or dependent 3 months after stroke. An occlusion of the main stem of the MCA within 6 h after stroke was an independent predictor for poor outcome (p=0·0006). 50% of patients with ultrasonographic diagnosis of branch occlusions and 63% with normal MCA had a good outcome. Combination of CT scan without early signs of infarction and a normal MCA resulted in a predictive value of 71% for a good functional outcome.**

Interpretation **Cerebrovascular ultrasonography provides additional functional prognostic information in the hyperacute stage of ischaemic stroke. The technique is practical in a well-resourced unit, can be used to identify patients with high risk for poor functional outcome, and thus would be an appropriate investigation for future trials.**

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Introduction

Standard assessment for a patient presenting with acute stroke includes medical history, clinical examination, and brain CT. Unfortunately, this approach provides no clear evidence whether a patient might benefit from potentially harmful thrombolytic treatment. This reasoning holds true, for example, for patients eligible for intravenous thrombolysis who have only mild or resolving symptoms. Barber and colleagues[1] suggested imaging of persistent vascular occlusion in this situation to identify patients likely to deteriorate without thrombolysis.[1,2] Conversely, there is a reluctance to give thrombolytics if a patient has a normal vessel patency. Assessment of vascular pathology and haemodynamics in patients with acute stroke is thought to enable early judgment of functional outcome and thrombolytic efficacy.[3]

In several small studies, transcranial doppler has shown that vessel patency can be adequately assessed and that ultrasound diagnosis of occlusion of the middle cerebral artery (MCA) is a good predictor of poor outcome.[4–9] By contrast with perfusion imaging, which is impractical in many centres, transcranial doppler is widely available. Compared with the widespread use of ultrasound in subacute and chronic cerebrovascular disease, application of transcranial doppler in the early stroke setting is unusual. The aim of the Neurosonology in Acute Ischemic Stroke (NAIS) study—an international multicentre project of the Neurosonology Research Group of the World Federation of Neurology—was to assess the prognostic value of early ultrasound diagnosis in addition to routine CT scan on admission and standard assessment of the neurological deficit. We postulated that patients with MCA occlusion would have a worse functional outcome than those with a patent artery, as determined by a dichotomised modified Rankin score.

Methods

Patients

Eligible patients were men and women older than 18 years who had a clinical diagnosis of MCA stroke, brain CT findings compatible with ischaemic stroke, a neurological deficit score of one or more on the National Institutes of Health Stroke Scale (NIHSS),[10] and for whom extracranial and transcranial ultrasound could be undertaken within 6 h after the onset of symptoms. Patients were excluded if they had a pre-existing clinical deficit that could interfere with the standard assessment of the acute ischaemic deficit, an inadequate temporal bone window, which did not allow bilateral transcranial sonography, or if sonography would have delayed

thrombolysis to be done in accordance with local standards.

Procedures

The detailed study design has been published elsewhere.[11] NAIS was undertaken in 18 centres in six European countries. Neurological deficit and functional disability was quantified at admission and on day seven according to the NIHSS, the modified Rankin scale (mRS), and the Barthel index (BI).[12,13] Disability was reassessed 90 days after stroke by telephone interview with the patient or a relative (mRS, BI). For primary and secondary outcome analyses the 90-day outcome was dichotomised into independence (including only mild disability; mRS 0–2) and dependence or death (mRS 3–6). Our primary analysis included those patients with a moderate to severe deficit (equivalent to 5–25 points on the NIHSS) on admission, because outcome is usually predictable for those with NIHSS less than five (good outcome expected) and more than 25 (severe disability expected).

Sonographic examination was done on admission in all study patients. Those with occlusion or severe stenosis of the internal carotid artery (ICA) or MCA on the symptomatic side were re-examined 6 h and 12–24 h after stroke onset. In patients admitted and initially examined before 3 h of symptom onset, additional sonographic re-examination was done at 3 h.

Ultrasound examination included doppler sonography of the orbital and supraorbital arteries, colour-coded duplex sonography with registration of blood-flow velocities, spectral doppler wave forms from the common carotid and extracranial ICA, and transcranial doppler or colour-coded duplex sonography from the intracranial ICA, MCA (M1/M2 segment), anterior cerebral (A1 segment), and posterior cerebral artery (P1 or P2 segment) undertaken bilaterally for each artery. Contrast enhancing agents were recommended in any case with insufficient signal intensity of one or both MCAs, especially in case of suspected occlusion. Occlusion of the MCA main-stem (proximal M1 segment) was diagnosed in the absence of a corresponding flow signal after contrast enhancement and visibility of other arteries of the ipsilateral anterior circulation during insonation from the side of the occluded artery. Diagnosis of carotid-T occlusion in the absence of corresponding flow signals (M1, distal ICA, A1) required detectable flow (if necessary after contrast enhancement) in the ipsilateral A2 segment or the contralateral anterior circulation when insonated from the side of the affected hemisphere, and was confirmed by additional extracranial internal-carotid occlusion or flow-velocity diminution of more than 50% compared with the contralateral side. Diagnosis of occlusion of a large branch or of multiple branches of the MCA was based on the asymmetry index of Zanette and co-workers.[9] This means a diminution of mean flow of the MCA of 21%. For a diagnosis of severe stenosis of the MCA (M1 segment) or the intracranial distal ICA, maximum peak systolic velocity must exceed 220 cm/s, corresponding to 5·5 kHz by transcranial doppler (2 MHz pulsed wave-probe).[14] Occlusion of the extracranial ICA at the bifurcation level is diagnosed if the artery can be visualised on B-mode image without detectable colour filling and doppler spectrum.[15] Maximum peak systolic velocities above 300 cm/s (angle corrected with insonation angle of ≤60°), corresponding to 10 kHz (4 MHz continuous wave-probe), are indicative of severe extracranial internal-carotid stenosis and were corroborated by additional indirect haemodynamic criteria.[16] The accuracy of ultrasound as compared with angiography used as the gold standard has been shown by Zanette and colleagues,[9] Baumgartner and colleagues,[14] and Gerriets and colleagues.[6]

CT was done on admission in all stroke patients to exclude intracerebral and intracranial haemorrhage. Brain imaging by CT or alternative MRI was repeated 2–8 days after stroke onset and was used to assess the location and extent of brain infarction. There was a central CT reading panel being informed only about the affected hemisphere. CT scans were assessed for early findings of cerebral ischaemia—ie, parenchymal hypoattenuation and focal swelling. Extension of the territory affected was graded according to the scoring system suggested by the ASPECTS study group.[17] They divided the territory of the MCA into ten areas (ten points). One point is subtracted for each area of early ischaemic change, such as focal swelling or parenchymal hypoattenuation. A baseline ASPECTS score of seven or less is deemed to discriminate independence against dependence and death 3 months after stroke.

For quality control each centre had to submit three complete case record files. Centres were accredited after review of the ultrasound documentation and case record file by the steering committee. All participating centres were experienced in ultrasound diagnostics. No special training was provided. All ultrasound examinations were undertaken by the stroke-unit physician. Enrolment of consecutive patients was intended either during working hours or on a 24 h basis depending on the local structure. Centres were requested to submit every case record file 7 days after inclusion. Every case record was reviewed (JA, GMvR) for inconsistencies before acceptance.

The trial protocol was reviewed and approved by the ethics committee of the Landesärztekammer Hessen, Germany, and by local ethics committees of each centre. The study was undertaken in accordance with the declaration of Helsinki.

Statistical analysis

The primary aim was to analyse the relation between MCA status and the outcome in patients with a moderate or severe acute ischaemic stroke (target group included

patients with NIHSS score 5–25). To do this we classified the MCA as being occluded (main-stem occlusion) or patent (normal, stenosis, branch occlusion). Similarly, outcome was dichotomised into good and poor outcomes on the basis of the mRS score.

We expected a 30% occlusion rate of the main stem of the MCA. Our power calculation, based on this assumption, was 200 patients in our target group. The reason to form a target group was to exclude patients with very mild symptoms who had a high probability of a good outcome as well as comatose patients with a poor prognosis. Under the assumption that only half the patients recruited would have an initial NIHSS score of 5–25, 400 patients had to be recruited. This sample size results in 80% power to detect a 20% difference in outcome of mRS score 0–2 in patients initially presenting with MCA occlusion compared with those with an open artery if the overall frequency of outcome of a mRS score 0–2 is about 40%.

Data are presented for continuous variables as number, arithmetic mean, SD, median, or IQR, and by way of group frequencies and percentages for categorical variables. Possible differences between groups were analysed by Fisher's exact test for nominal or categorical variables and by the Mann-Whitney *U* test for continuous variables. Multivariate logistic regression techniques were used to investigate the possible predictive value of MCA status, patent versus occluded, for the outcome measured by mRS to enable adjustment for potential confounding. The following possible confounders were investigated for their association with outcome: previous stroke, previous amaurosis fugax, previous transient ischaemic attack, previous myocardial infarction, atrial fibrillation, arterial hypertension, heart-valve disease, hypercholesterolaemia, diabetes mellitus, smoking, alcohol consumption, current contraceptive medication in women, NIHSS on admission, ASPECT score, and centre. For the analysis the 11 smaller centres were combined. The result is presented as an odds ratio with corresponding 95% CI. All calculations have been done with SAS version 8.2 (Cary, North Carolina, USA).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 18 centres recruited 452 white patients from April, 2000, to October, 2002. All patients completed the 7 day follow-up and 434 patients (98%) completed the 3 month follow-up. 444 of 452 patients were investigated initially by CT scan and eight by MRI. 361 patients had an initial moderate to severe clinical deficit (NIHSS 5–25) and represented the target group for the primary analysis (table 1).

	Target group
Age, years	66·1 (12·5)
Men	238 (66%)
Median NIHSS score (IQR)	13 (8–18)
Time from first symptoms to ultrasound examination, min	187 (95)
Arterial hypertension	237 (65%)
Atrial fibrillation	100 (28%)
TIA or previous stroke	95 (26%)
Cigarette smoking	121 (34%)
Hyperlipidaemia	110 (31%)
Diabetes	80 (22%)

Data are mean (SD), number (%), unless otherwise stated. TIA=transient ischaemic attack.

Table 1: **Baseline characteristics**

Transcranial sonography of the target group at baseline showed main-stem MCA occlusion in 57 (16%) patients, branch occlusions in 176 (48%), and main-stem MCA stenosis in seven (2%). In 121 (34%) patients the examination was normal. Table 2 shows the patients' characteristics.

CT scans were available for 344 of the 361 patients from the target group. The initial CT scan quantified by the ASPECTS score revealed early ischaemic signs in 192 (56%) patients; in 108 (31%) patients the ASPECTS value was seven or less. The follow-up assessment, undertaken 4·8 days (SD 2·6) after admission, showed brain infarction in the anterior circulation of 268 (78%) patients.

Patients with occlusion of the MCA, diagnosed 6 h after stroke, were significantly more likely to have an unfavourable clinical outcome than were those with a patent MCA (relative risk 1·96, 95% CI 1·63–2·17). In

	MCA normal (n=121)	MCA branch occlusion (n=176)	MCA main-stem occlusion (n=57)
Age, years	66·6 (12·3)	64·9 (12·3)	69·3 (12·9)
Men	80 (66%)	118 (67%)	40 (70%)
Median NIHSS score (IQR)	9 (6–12)	13 (8–17)	19 (16–22)
Severe ipsilateral extracranial disease	13 (11%)	67 (38%)	29 (51%)
Time from first symptoms to first ultrasound examination, min	181 (90)	199 (99)	175 (89)
Cigarette smoking	40 (33%)	65 (37%)	14 (25%)
Diabetes	25 (21%)	42 (24%)	11 (19%)
Arterial hypertension	85 (70%)	112 (64%)	36 (63%)
Atrial fibrillation	32 (26%)	44 (25%)	23 (40%)
TIA or previous stroke	38 (31%)	41 (23%)	15 (26%)

Data are mean (SD) or number (%), unless otherwise stated. TIA=transient ischaemic attack. Patients with MCA stenosis are excluded (n=7).

Table 2: **Vascular status and patients' characteristics**

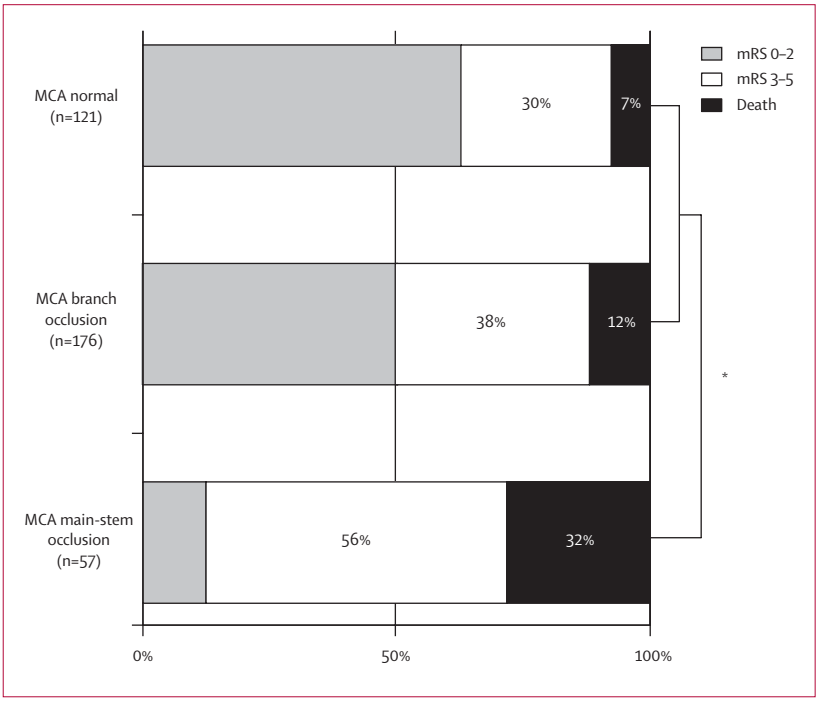

***Figure*: Outcome at 3 months for different ultrasound findings of the MCA**
Side-to-side differences for branch occlusion and main-stem MCA occlusion, dichotomised in mRS≤2 and mRS>2 for patients with normal MCA findings. Patients with high-graded MCA stenosis were excluded (n=7). Patients with extracranial carotid pathology were not excluded. *p<0·0006 after logistic regression analysis for age, initial NIHSS, admission CT, centre, and risk factors.

patients with main-stem MCA occlusion, only 12% showed a favourable outcome (mRS 0–2), compared with 55% of those with patent MCA including branch occlusions (figure). The difference is even greater when patients without any pathology in the MCA are compared with those with proximal MCA occlusion. This finding was confirmed as an independent predictor of outcome even after adjustment for age, initial NIHSS score, ASPECT score, centre, and risk factors (odds ratio 5·5, 95% CI 2·1–14·6, p=0·0006). The outcome was also significantly affected by the following factors: age (4·5, 2·4–8·2), NIHSS score on admission (3·4, 1·6–7·4), ASPECT score (2·6, 1·4–4·9), previous stroke (2·3, 1·1–5·0), and one centre (3·6, 1·2–11·2). Further risk factors and the other centres did not significantly affect the outcome.

63% of the patients with a patent MCA excluding branch occlusions had a favourable outcome at 3 months. Combining the criteria of CT scan without early signs of infarction and patent MCA without any pathology, the rate of favourable outcome increased to 71%.

44 patients had unfavourable outcome (mRS >2) despite normal MCA findings in the sonographic examination 6 h after stroke onset. Of these patients, 37 had follow-up CT scans. They showed large infarctions (ASPECTS ≤7) in 17 patients and smaller ones in 16 patients. In four patients no infarction was seen on follow-up CT scan. Six patients with ASPECTS value of eight or more revealed small isolated infarctions of the basal ganglia, including the internal capsula, and in ten cases small MCA-branch infarctions. Stroke and transient ischaemic attack at follow-up were observed in only 15 of 434 patients (3·5% stroke recurrence rate in 3 months).

Discussion

We postulated that we would identify a more than 20% difference in outcome 3 months after stroke as measured by the mRS when comparing patients with occluded versus patent MCA (including those with branch occlusions). We actually found a difference of 43%. The difference was even higher (51%) between an occluded versus a patent MCA without signs of branch occlusions. In the case of MCA occlusion, unfavourable outcome was seen in 88% of patients. This finding accords with those of previous single-centre studies.[4,7,8] The ultrasound diagnosis remained an independent predictor after adjustment for age, severity of the neurological deficit at admission, CT finding at admission, and risk factors. The rate of a favourable outcome in the presence of normal MCA findings was rather low (63%). Combining the criteria of a CT scan without early signs of infarction on admission and a normal MCA finding this rate improved to 71%. In the studies of Goertler and colleagues[7] and Baracchini and co-workers[4] a patent MCA was more clearly associated with a favourable outcome than in our study. This could be due to different frequencies of stroke subtypes.

Unfavourable outcome despite patent arteries could be due to five relevant circumstances. First, conditions not affecting the haemodynamics of large vessels, such as strategic lacunar infarction or small infarctions in the territory of a single branch. Two of three infarctions found in this group were small (ASPECTS score ≥7). Second, recanalisation before the ultrasound examination. This can be assumed in cases of large infarctions in the presence of a normal MCA finding—eg, 6 h after stroke. This was the second most frequent factor. Third, infarction in the vertebrobasilar territory mimicking MCA infarction.[18] Fourth, secondary symptomatic haemorrhage. Fifth, recurrent stroke or other diseases during follow-up. The possibility of stroke recurrence during follow-up has been discussed as a confounding factor, especially in patients with expected good outcome (patent vessels). Stroke and transient ischaemic attack at follow-up was observed in only 15 of 434 patients (3·5% stroke recurrence rate in 3 months). Therefore, the effect of recurrence on the outcome in general was rather low.

The high frequency of combined intracranial and extracranial severe lesions was surprising (table 2); however, this finding was similar to those of Baracchini[4] based on ultrasound diagnosis and Fischer and colleagues[19] based on immediate digital subtraction angiography with 30% ICA occlusions.

The availability of a trained sonographer round the clock on the stroke unit is generally seen as a limitation. The large number of patients included was achieved by including centres that have incorporated an ultrasound examination into their routine admission procedures. Obviously it is a precondition that there are well-trained staff and an ultrasound device placed in the emergency room or in the stroke unit. The examination protocol had to be shortened and, for this study, focussed on the anterior circulation to save time.[20] Transcranial doppler sonography on the other side is limited in about 10–20% of acute stroke examinations by transmission problems through the skull.[21] This rate can be reduced by the application of contrast enhancement to 7%.[6] An inadequate acoustic bone window was an exclusion criterion for the NAIS study and therefore cannot be quantified.

At present several diagnostic methods compete for imaging of cerebral arteries in acute stroke. They differ in the quality of vascular imaging, feasibility, and costs. The attraction of ultrasonography is the possibility of rapid and repeated assessments.

This NAIS study has shown the substantial prognostic power of ultrasonography. The application of potentially harmful treatments should be based on the expected outcome. It is unlikely that the effect of thrombolysis is independent of the vascular status. Therefore, vascular imaging is particularly recommended for patients who are rapidly improving as advocated by Barber and colleagues.[2] In the 3–6 h window the ultrasound diagnosis could be used as a screening method to detect persistent occlusions. This approach could identify patients who might benefit from interventional treatment.[22]

Contributors

JA participated in the study design, reviewed case records, analysed data, and drafted the manuscript. MG participated in the study design and analysed data. G-MvR planned and coordinated the study, participated in the study design, reviewed case records, and analysed data. All authors contributed to the discussion and interpretation of the results.

Conflicts of interest

We have no conflicts of interest.

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Steering committee

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Participating centres

Participating centres with at least three enrolled patients, in the order of the number of included patients, are listed below: Asklepios Neurologische Klinik, Nidda Bad Salzhausen, Germany (G-M von Reutern, A Wassner, D Degner, C Fritzsch, J-P Garczarek, B Rossmanith, N Rogalskich, I Worm; 100 patients); Department of Neurology, University of Magdeburg, Germany (M Goertler, T Blaser, K Haupt, S Guhr, S Krueger, M Wunderlich, T Treuheit, J Heisinger, A Glaenzel, H Lotze; 63 patients); Department of Neurology, University of Giessen, Germany (M Kaps, J Allendoerfer, D Degner, E Stolz, M Jauss; 53 patients); Department of Neurology, Ostrava Faculty Hospital, Ostrava, Czech Republic (M Bar, D Skoloudik, P Hradilek; 41 patients); Department of Neurology, Asklepios Schildautalklinik Seesen, Germany (R Brodhun, S Biethahn, G Kuehnel; 38 patients); Department of Neurology, Städtische Kliniken Dortmund, Germany (G Dittmar; 38 patients); Department of Neurology, Zentralkrankenhaus Bremen Ost, Germany (F Brunner-Beeg, K Wittig, S Dempewolf; 30 patients); Department of Neurology, University of Freiburg, Germany (A Hetzel, E Oehm; 13 patients); Neurovascular Unit, C Mondino Foundation, University of Pavia (D Bosone, G Micieli; 11 patients); Department of Neurology, Horst-Schmidt-Kliniken Wiesbaden, Germany (J Huewel, M Wagner-Heck; 10 patients); Department of Neurology, Blessed Mary Anthony Hospital, Ostrava, Czech Republik (D Vaclavik; 10 patients); Department of Neurology, University Hospital of Zagreb, Croatia (V Demarin, A Lovrencic-Huzjan; 9 patients); Department of Neurology, Regio Emilia, Italy (G Malferrari; 9 patients); Department of Neurology, San Benedetto del Tronto, Italy (S Sanguigni, L Caratola, T Carboni, R Gobatto; 7 patients); Department of Neurology, Bezirkskrankenhaus Günzburg, Germany (B Widder, A Wiborg; 6 patients); Department of Neurology, University Hospital of Graz, Austria (K Niederkorn, S Horner, D Svetina; 5 patients); Geriatric Hospital Ancona, Italy (O Scarpino; 5 patients); Department of Neurology, University of Frankfurt, Germany (M Sitzer, A Wassner; 4 patients).

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